PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	To condition or not condition? Analyzing “change” in longitudinal randomized controlled trials
AUTHORS	Coffman, Cynthia; Edelman, David; Woolson, Robert

VERSION 1 - REVIEW

REVIEWER	G. Frank Liu Merck & Co. Inc., USA.
REVIEW RETURNED	22-Jul-2016

GENERAL COMMENTS	The paper compares a few commonly used statistical models for analysis of repeated measures with adjustment of baseline. Conditional approach includes ANCOVA model where treatment comparison is conditional on baseline, while unconditional models include longitudinal data analysis with or without constraint at baseline. Motivated from a real clinical trial analysis where the results from ANCOVA and cLDA produced different conclusions.The paper clarifies some statistical properties of this models with respect to assumption and missing data handling. It is concluded that cLDA would be the method of choice because it produces efficient and robust estimates under reasonable missing data assumptions. The methods presented in the paper should be very interesting to scientists including biostatisticians in the clinical trial field in analysis longitudinal trials with missing data. The paper is generally well written. Some specific comments for consideration are as follows: 1) Page 4, lines 39-44, consider to split the long sentence for “Typically, …, vector” to make it easier to understand and follow. 2) Page 6, line 17, the response profile modeling is also called mixed model repeated measures (MMRM) in clinical trial literatures (e.g., Mallinckrodt et al 2008 Drug Information Journal pp303-319). It will be good to point out this connection here. 3) Pages 7 to 8, suggest to use unique notations for each effect. For example, may use ‘beta’ for ‘gamma’ on page 7; use ‘delta’ for ‘gamma tau’. The ‘gamma tau’ may be confused with the multiply of those two parameters. 4) Page 10, line 38 (end of Methods section), please add a sentence to state what is the covariance matrix used in cLDA and LDA. I assumed that unstructured covariance has been used in those models. 5) Page 13, line 2, it may be good to add a few sentences to point out that: comparing the results for Post-only with completers in Table 1 to that in Table 2, there were 9 patients had missing baseline. The clear difference between those two estimates may imply that those who dropped out after baseline (i.e. had baseline values only) may not be a completely random sample from the study population (i.e.,

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	MCAR may not be true in this example). Similarly, the results from LDA with completers were quite different from the LDA with all available data, which also implies the completers may not be a random sample of the study population. So analysis based on completers (including the ANCOVA model) may be biased. As a result, the highly significant analysis from ANCOVA model might be misleading due to inappropriate handling of missing data. 6) Page 23, the assumption of equal variance at baseline and post-treatment may be required for all derived formulas. So it will be good to state that at the beginning instead of within LDA model.

REVIEWER	Isabel E. Allen UCSF, USA
REVIEW RETURNED	29-Aug-2016

GENERAL COMMENTS	I like this paper but I would like to see more discussion of the applications of the technique or some additional recommendations from the authors perhaps related to specific study designs. Since the simplest analysis is a pre-post test, it wasn't clear to me if your Post-only analysis is this paired analysis or not. Also, given that you looked at only one dataset, what are the limitations of your specific example and how might they differ for different datasets?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: G. Frank Liu
Institution and Country: Merck & Co. Inc., USA.
Please state any competing interests: None declared.

Please leave your comments for the authors below
The paper compares a few commonly used statistical models for analysis of repeated measures with adjustment of baseline. Conditional approach includes ANCOVA model where treatment comparison is conditional on baseline, while unconditional models include longitudinal data analysis with or without constraint at baseline. Motivated from a real clinical trial analysis where the results from ANCOVA and cLDA produced different conclusions.The paper clarifies some statistical properties of this models with respect to assumption and missing data handling. It is concluded that cLDA would be the method of choice because it produces efficient and robust estimates under reasonable missing data assumptions.

The methods presented in the paper should be very interesting to scientists including biostatisticians in the clinical trial field in analysis longitudinal trials with missing data. The paper is generally well written. Some specific comments for consideration are as follows:

1) Page 4, lines 39-44, consider to split the long sentence for “Typically, …, vector” to make it easier to understand and follow.
--Sentence has been revised to clarify.
2) Page 6, line 17, the response profile modeling is also called mixed model repeated measures (MMRM) in clinical trial literatures (e.g., Mallinckrodt et al 2008 Drug Information Journal pp303-319). It will be good to point out this connection here.
--Reference to MMRM has been added.
3) Pages 7 to 8, suggest to use unique notations for each effect. For example, may use ‘beta’ for

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‘gamma’ on page 7; use ‘delta’ for ‘gamma tau’. The ‘gamma tau’ may be confused with the multiply of those two parameters.
--Notation to clarify models has been done.
4) Page 10, line 38 (end of Methods section), please add a sentence to state what is the covariance matrix used in cLDA and LDA. I assumed that unstructured covariance has been used in those models.
--Yes, cLDA and LDA models were fit with unstructured covariance, this was added in the Methods.
5) Page 13, line 2, it may be good to add a few sentences to point out that: comparing the results for Post-only with completers in Table 1 to that in Table 2, there were 9 patients had missing baseline. The clear difference between those two estimates may imply that those who dropped out after baseline (i.e. had baseline values only) may not be a completely random sample from the study population (i.e., MCAR may not be true in this example). Similarly, the results from LDA with completers were quite different from the LDA with all available data, which also implies the completers may not be a random sample of the study population. So analysis based on completers (including the ANCOVA model) may be biased. As a result, the highly significant analysis from ANCOVA model might be misleading due to inappropriate handling of missing data.
--We have added text to make this point about potential bias becausethe implication from comparing completers-to-analysis with all participants indicates completers are not a random sample of the study population.
6) Page 23, the assumption of equal variance at baseline and post-treatment may be required for all derived formulas. So it will be good to state that at the beginning instead of within LDA model.
--We have moved this statement to the beginning of the section.

Reviewer: 2
Reviewer Name: Isabel E. Allen
Institution and Country: UCSF, USA
Please state any competing interests: None declared

Please leave your comments for the authors below
I like this paper but I would like to see more discussion of the applications of the technique or some additional recommendations from the authors perhaps related to specific study designs. Since the simplest analysis is a pre-post test, it wasn't clear to me if your Post-only analysis is this paired analysis or not. Also, given that you looked at only one dataset, what are the limitations of your specific example and how might they differ for different datasets?

--The specific design that we are discussing in this paper are longitudinal randomized controlled trials with a baseline assessment followed by a few longitudinal assessments. Our recommendation for studies of this type of design is to use cLDA models as they are straightforward to implement and under reasonable missing data assumptions yield unbiased estimates of treatment effects and inferential statistics.

We attempted to include all types of analysis methods that can be applied to data of this type and to simplify by using a design with just a pre- and a post period. As you note one type of analysis that can be done is to ignore the pre- or baseline value and only look at differences between treatments of the mean POST period estimates; this was our SPO (Simple Post Only) analysis. The SACS (Simple Change Score analysis) is the paired analysis that you describe above.

Our goal in this paper was to use a data set to illustrate the statistical theory that has been developed to demonstrate the potential implications of an inappropriate analysis. We are not limited by this data set, this data set illustrates what can happen when missing data assumptions are more complex and methods of analysis do not account for this complexity as well as known issues of precision and

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power for change score type methods. It is true that these methods will not diverge for every data set that they would be applied to – however as missing data assumptions cannot specifically be tested cLDA models are the optimal choice across a range of conditions. We have included additional text in the Missing Data Implications section to elaborate.

VERSION 2 – REVIEW

REVIEWER	Isabel E. Allen University of California, San Francisco, USA
REVIEW RETURNED	12-Oct-2016

GENERAL COMMENTS	The revision has addressed all the issues raised in the earlier reviews

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